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The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks

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Tinnitus is the perception of a sound in the absence of an external sound source. It is characterized by sensory components such as the perceived loudness, the lateralization, the tinnitus type (pure tone, noise-like) and associated emotional components, such as distress and mood changes. Source localization of quantitative electroencephalography (qEEG) data demonstrate the involvement of auditory brain areas as well as several non-auditory brain areas such as the anterior cingulate cortex (dorsal and subgenual), auditory cortex (primary and secondary), dorsal lateral prefrontal cortex, insula, supplementary motor area, orbitofrontal cortex (including the inferior frontal gyrus), parahippocampus, posterior cingulate cortex and the precuneus, in different aspects of tinnitus. Explaining these non-auditory brain areas as constituents of separable subnetworks, each reflecting a specific aspect of the tinnitus percept increases the explanatory power of the non-auditory brain areas involvement in tinnitus. Thus, the unified percept of tinnitus can be considered an emergent property of multiple parallel dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature.

Keywords: EEG, non-auditory brain areas, emergent property, multiple parallel overlapping subnetworks

INTRODUCTION

Consciousness is a crucial aspect of being human. One specific component of consciousness is the conscious perception of auditory stimuli. Hearing is a crucial sensory domain that helps to localize as well as recognize a sound source and is essential for communication. Our auditory function helps us to understand the world, maintain social contacts and to detect dangerous situations. In humans and other vertebrates, hearing is performed primarily by the auditory system. Vibrations are detected by the ear and translated into nerve impulses that are processed by the auditory cortex. Recent research has shown, however, that activity in the primary auditory cortex is necessary, but not sufficient condition for an auditory stimulus to gain access to consciousness (Boly et al., 2004). It has recently become clear that in order to perceive an auditory percept, hierarchically higher-order multimodal association areas are required (Boly et al., 2004; Laureys, 2005), similarly to what has been proposed in the visual (Dehaene et al., 2006) and somatosensory system (Laureys et al., 2002; Boly et al., 2005).

Understanding the brain mechanisms involved in the simplest forms of auditory conscious perception, such as noise and tones from the environment (i.e., externally generated) is a crucial start for gaining knowledge about auditory consciousness specifically and consciousness at large. However, a sound can also be internally generated. That is, perceiving a sound in the absence of an external sound source. This phenomenon is also known as tinnitus. In most cases this phantom sound resolves spontaneously within seconds or minutes. However, tinnitus persists in 5–10% of the population in western countries (Heller, 2003; Eggermont and Roberts, 2004), and interferes severely with the quality of life in 5–26% within this tinnitus population (Axelsson and Ringdahl, 1989; Heller, 2003). Moreover, the prevalence of chronic tinnitus increases with age, peaking at 14.3% in people between 60 and 69 years of age (Shargorodsky et al., 2010).

Phenomenologically, tinnitus can be perceived unilaterally or bilaterally and characterized as a pure tone, a narrow band noise or polyphonic. Tinnitus is usually evaluated both for its perceived loudness and annoyance or distress level. Yet, not everyone who experiences tinnitus becomes chronically distressed and measures of tinnitus loudness rarely correlate with experienced distress (Andersson and Westin, 2008). Distress can play an important part in the development of tinnitus, as distress might act as a potential trigger for sudden hearing loss and onset of tinnitus, but is not a necessity (Schmitt et al., 2000). Distress might unfavorably influence habituation via hyperarousal processes, but is not a requirement (Hallam, 1996). Tinnitus symptoms themselves can act as a stressor resulting in higher physiological arousal and psychological distress, but this is not always the case (Alpini and Cesarani, 2006).

In this review we try to map and disentangle the different brain areas generating an auditory phantom percept. We will only focus on simple auditory phantom percepts such as tones and noise and not on more complex sounds such as hearing voices or music. Although very common, tinnitus is not well understood. Clinical data indicate the involvement of peripheral auditory structures in tinnitus (Nicolas-Puel et al., 2002). This is suggested by the

fact that tinnitus is often related to damage of the cochlea or the auditory nerve such as in presbyacusis, noise induced hearing loss, drug-related hearing loss, Meniere's disease, or other inner ear pathologies (Lockwood et al., 2002). Furthermore it has been demonstrated that psychoacoustic characteristics of tinnitus like pitch overlap with the frequency spectrum of an individual's hearing loss (Norena et al., 2002; Norena and Eggermont, 2003, 2006). In addition in animal models it was revealed that a peripheral mechanism involving the N-methyl-D-aspartate (NMDA) glutamatergic receptors in the cochlea can be generator of tinnitus (Guitton et al., 2003). On the other hand, an increasing amount of data shows the role played by activation and remodeling of various central cortical or subcortical structures to cause or to perpetuate tinnitus symptomatology (Muhlnickel et al., 1998; Eggermont and Roberts, 2004; Eggermont, 2005; Weisz et al., 2005). Investigating the neurophysiological differences in the characteristics of tinnitus perception could lead to a better understanding of pathological auditory neural activity. Therefore, we first discuss the different auditory and non-auditory brain areas involved in tinnitus and their potential function within the tinnitus network. Secondly, we try to combine these different brain areas involved in tinnitus in a multiple brain subnetworks.

THE AUDITORY AND NON-AUDITORY BRAIN AREAS INVOLVED IN TINNITUS

Based on previous quantitative electroencephalography (qEEG) research the following areas have been implicated in tinnitus: the auditory cortex, the subgenual and dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex, the insula, the supplementary motor area, the orbitofrontal cortex (including the inferior frontal gyrus), the posterior cingulate cortex, the precuneus and the parahippocampus. **Table 1** and **Figure 1** give an overview of the different brain areas obtained based on qEEG research in tinnitus and their involvement in specific tinnitus characteristics.

THE AUDITORY CORTEX

Animal experiments have demonstrated that the degree of behavioral importance of an external sound is related to the representational expansion of its frequency in the primary auditory cortex (Rutkowski and Weinberger, 2005), and that the auditory cortex is involved in tinnitus (Engineer et al., 2011). But also in humans it was shown that the auditory cortex plays a role in tinnitus (van der Loo et al., 2009). In comparison to a control group both left and right-sided tinnitus patients had an increased gamma band activity in both the left and right primary and secondary auditory cortex (Vanneste et al., 2011a). This is the reason why primary and secondary auditory cortices are considered as important potential targets for the treatment of tinnitus (De Ridder et al., 2006a, 2007a,b). The rationale is that this phantom sound might be related to an increased neuronal activity within the auditory cortex secondary to the imbalance between excitatory and inhibitory mechanisms or an adjustment of auditory gain mechanisms (Norena, 2011). The difference could be triggered by altered auditory inputs which may support functional reorganization in synaptic connections. Neural hyperactivity has been found in subcortical structures (cochlear nuclei, inferior colliculi, medial geniculate bodies) and auditory cortical regions (primary and secondary auditory cortex) in animal models of tinnitus and hearing loss (Jastreboff and Sasaki, 1986; Jastreboff, 1990; Brozoski et al., 2002).

Based on MEG data, thalamocortical dysrhythmia has been proposed as a pathophysiological model for the development of gamma band activity related to the tinnitus percept (Llinás et al., 1999). According to this model tinnitus is caused by an abnormal, spontaneous, and constant gamma band activity (>30 Hz) generated as a consequence of hyperpolarization of specific thalamic nuclei, in casu the medial geniculate body. In normal circumstances auditory stimuli increase thalamocortical rhythms to gamma band activity (Joliot et al., 1994). In the deafferented state, however, oscillatory activity decreases from resting state alpha activity (8–12 Hz) to theta band activity (4–7 Hz) (Steriade, 2006). As a result, lateral inhibition is reduced inducing a surrounding gamma band activity known as the "edge effect" (Llinás et al., 1999, 2005). Lorenz et al. (Lorenz et al., 2009) reported an inverse relationship between alpha and gamma activity over subjects calculated for sources seeded in auditory regions. The inverse relationship was presented for tinnitus and control tinnitus group. Synchronized gamma band activity in the auditory cortex is proposed to bind auditory events into one coherent conscious auditory percept (Ribary et al., 1991; Tiitinen et al., 1993; Joliot et al., 1994; Llinas et al., 1994, 1998; Crone et al., 2001). In addition it was found that tinnitus perceived loudness is correlated to increased contralateral gamma band activity in the auditory cortex indicating that gamma band activity is important in tinnitus (van der Loo et al., 2009).

THE PARAHIPPOCAMPUS

The differences between uni- and bilateral tinnitus are reflected by high frequency EEG activity (i.e., beta and gamma) in the parahippocampus (Vanneste et al., 2011c). That is, unilateral tinnitus patients showed increased high frequency activity in the right parahippocampal area. This same brain area is also involved at an alpha rhythm in patients with a high distress and in non-coping with tinnitus. In addition, based on a region of interest analysis, whether tinnitus is perceived on the left side or right side tinnitus is dependent on gamma-band activity of the contralateral parahippocampal area (Vanneste et al., 2011c). In contrast to expectation, for the auditory cortex no differences were found between left-sided and right-sided tinnitus patients. In addition, narrow band noise tinnitus patients have increased activity in the parahippocampal area in comparison to pure tone tinnitus patients at the gamma frequency band (Vanneste et al., 2010a).

The involvement of the parahippocampus in tinnitus might be related to the constant updating of the tinnitus percept from memory thereby preventing habituation (De Ridder et al., 2006b). The posterior parahippocampal area is involved in auditory habituation as demonstrated by electrophysiological studies of auditory sensory gating both in animals (Bickford et al., 1993) and humans implanted with electrodes in the parahippocampus and hippocampus for epilepsy monitoring (Boutros et al., 2008). The hippocampal involvement in tinnitus pathophysiology is also demonstrated by histopathological findings of posterior hippocampus lesions in patients, who experience

Table 1 | Overview results based on resting-state EEG in tinnitus patients.

Brain region	BA	Function	Frequency band	Ref
Auditory cortex	BA21	Control group < Left and Right-sided tinnitus	gamma	Vanneste et al., 2011a
	BA22	Tinnitus with recent onset < Chronic tinnitus	gamma	Vanneste et al., 2011b
	BA40	Control group < Left and Right-sided tinnitus	gamma	Vanneste et al., 2011a
	BA41	Positive correlation with tinnitus intensity	gamma	van der Loo et al., 2009
Parahippocampus	BA36	Low distress < High distress	alpha1, alpha2	Vanneste et al., 2010b
	BA37	Coping with tinnitus < Non-coping	alpha1 alpha2	Vanneste et al., 2010b
	BA19	Left-sided tinnitus > Right-sided Tinnitus (right)	gamma	Vanneste et al., 2011a
		Left-sided tinnitus < Right-sided Tinnitus (left)	gamma	Vanneste et al., 2011a
		Control group < Left and Right-sided tinnitus	gamma	Vanneste et al., 2011a
		Pure tone < Narrow band noise tinnitus	gamma	Vanneste et al., 2010a
		Control group < Narrow band noise tinnitus	beta3, gamma	Vanneste et al., 2011c
		Unilateral tinnitus < Bilateral tinnitus		
Anterior cingulate cortex				
Dorsal	BA24	Tinnitus with recent onset < Chronic tinnitus	beta2, beta3	Vanneste et al., 2010b
	BA32	Control group < High distress	delta, theta	Vanneste et al., 2010b
		Control group > High distress	alpha, beta	Vanneste et al., 2010b
		Correlation with distress	alpha, beta	De Ridder et al., 2011b
Subgenual	BA25	Low distress < High distress	alpha1, alpha2	Vanneste et al., 2010b
		Coping with tinnitus < Non-coping	alpha1, alpha2	Vanneste et al., 2010b
		Correlation with TQ	alpha, beta	De Ridder et al., 2011b
DLPFC	BA9	Low distress coping > High distress coping	alpha1, alpha2	Vanneste et al., 2010b
	BA46			
Insula	BA13	Tinnitus with recent onset < Chronic tinnitus	beta3	Vanneste et al., 2011b
		Coping with tinnitus < Non-coping with tinnitus	alpha1, alpha2	Vanneste et al., 2010b
		Correlation with TQ and activity (left)	theta, alpha, gamma	van der Loo et al., 2011
		Correlation between TQ and activity (right)	delta, gamma	van der Loo et al., 2011
Supplementary motor area	BA6	Tinnitus with recent onset < Chronic tinnitus	theta	Vanneste et al., 2011b
	BA8	Low distress coping tinnitus > High distress coping	alpha1, alpha2	Vanneste et al., 2010b
		Unilateral tinnitus < Bilateral tinnitus	delta	Vanneste et al., 2011c
		Control group < Unilateral tinnitus	gamma	Vanneste et al., 2011c
		Control group < Bilateral tinnitus	gamma	Vanneste et al., 2011c
Orbitofrontal cortex	BA10	Pure tone > Narrow band noise tinnitus	delta	Vanneste et al., 2010a
(Inferior frontal gyrus)	BA11	Unilateral tinnitus > Bilateral tinnitus	delta	Vanneste et al., 2011c
	BA47	Control group < Bilateral tinnitus	beta3	Vanneste et al., 2011c
Posterior cingulate cortex	BA23	Low distress > High distress	alpha2	Vanneste et al., 2010b
		Pure tone < Narrow band noise tinnitus	beta3	Vanneste et al., 2010a
		Control group < Narrow band noise tinnitus	beta3	Vanneste et al., 2010a
		Control group Pure tone tinnitus	beta3, gamma	Vanneste et al., 2010a
Precuneus	BA7	Low distress > High distress	alpha2	Vanneste et al., 2010b
		Coping with tinnitus > Non-coping with tinnitus	alpha1, alpha2	Vanneste et al., 2010b
		Low distress coping tinnitus < High distress coping	alpha2	Vanneste et al., 2010b

DLPFC, dorsal lateral prefrontal cortex; Ref, reference.

tinnitus as a symptom of methyltin intoxications (Rey et al., 1984; Kreyberg et al., 1992). Furthermore, supraselective amytal injection in the anterior choroidal artery that supplies the amygdalohippocampal area is capable to suppress the pure tone component of tinnitus transiently by suppressing local activity (De Ridder et al., 2006b). The parahippocampal area together with the posterior cingulate cortex activity might be load dependent, as noise-like tinnitus constitutes multiple frequencies in contrast to pure tone tinnitus (Vanneste et al., 2010a). Hence, it has been proposed that a fundamental function of the (para)hippocampal structures is the establishment of auditory memory for tinnitus (Shulman, 1995).

THE DORSAL ANTERIOR CINGULATE CORTEX

A recent study, using source localization in EEG, revealed that distress in tinnitus patients is related to increased beta activity in the dorsal part of the anterior cingulate cortex and the amount of distress correlates with an alpha activity in several brain areas such as the amygdala, anterior cingulate cortex, insula, and parahippocampus (Vanneste et al., 2010b). A comparison

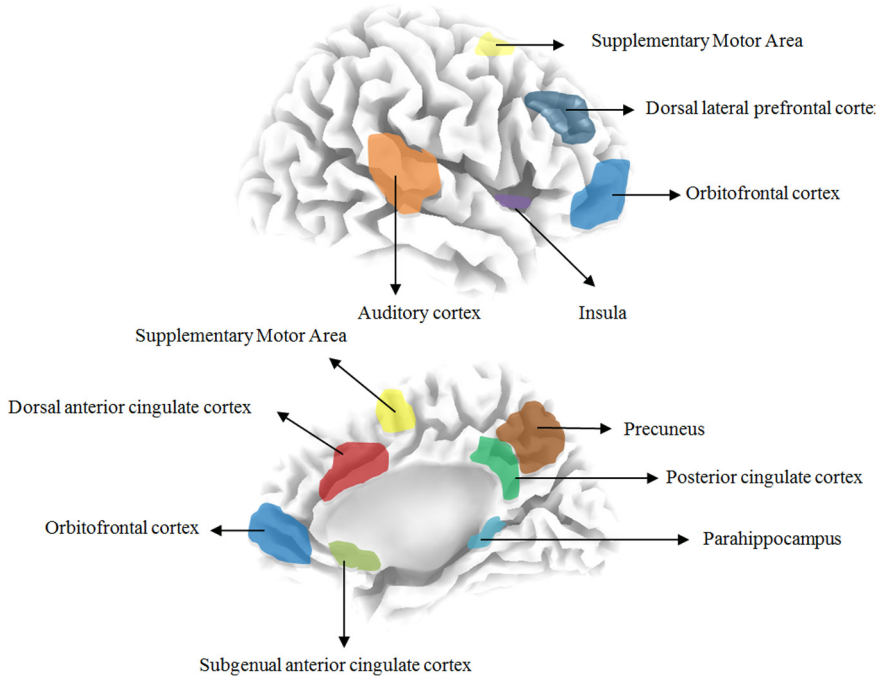

FIGURE 1 | Overview the different brain areas based on resting state EEG in tinnitus patients.

between recent onset and chronic tinnitus is related to differential activity and connectivity in a network comprising the auditory cortices, insula, dorsal anterior cingulate cortex and premotor cortex. Based on a blind source separation technique, tinnitus can be characterized by at least four independent components, two of which are posterior cingulate based, one based on the subgenual anterior cingulate and one based on the parahippocampus (De Ridder et al., 2011b). Only the subgenual component correlates with distress. When compared to a normative sample, group independent components analysis reveals that distress is characterized by two anterior cingulate based components. Spectral analysis of these components demonstrates that distress in tinnitus is related to alpha and beta changes in a network consisting of the subgenual anterior cingulate cortex extending to the pregenual and dorsal anterior cingulate cortex as well as the ventromedial prefrontal cortex/orbitofrontal cortex, insula, and parahippocampus. This network overlaps partially with brain areas implicated in distress in patients suffering from pain, functional somatic syndromes and, posttraumatic stress disorder, and might, therefore, represents an aspecific distress network. The dorsal part of the anterior cingulate cortex is one of the possible generators of frontal midline theta (Asada et al., 1999). Furthermore, it has been established that frontal midline theta oscillations are involved in attentional processes (Inanaga, 1998), and that both sympathetic and parasympathetic indices are increased during the appearance of frontal midline theta (Kubota et al., 2001). Whenever new information is presented, activity levels of the dorsal anterior cingulate cortex reflect the salience of the new information for predicting future outcomes (Critchley, 2005; Behrens et al., 2007), guiding optimal decision-making in an uncertain world (Kennerley et al., 2006). The human dorsal anterior cingulate cortex has developed a parallel specialization for motivational drive via a thalamocortical pathway relaying in the mediodorsal thalamus (Craig, 2002). Thus, the dorsal anterior cingulate might be involved in persisting attention to the tinnitus (Vanneste et al., 2010b; De Ridder et al., 2011b).

THE SUBGENUAL ANTERIOR CINGULATE CORTEX

The subgenual anterior cingulate cortex extending into nucleus accumbens-ventral tegmental area is involved in processing of aversive sounds (Zald and Pardo, 2002) and unpleasant music (Blood et al., 1999) as well as tinnitus (Muhlau et al., 2006). It has been implicated as the key component of social distress (Masten et al., 2009). This area in animals has been considered a visceromotor cortex, due to its connections with the parasympathetic nucleus tractus solitaries (Frysztak and Neafsey, 1994) and the sympathetic areas in the periaquaductal gray (Ongur and Price, 2000). Furthermore, it is functionally connected to the amygdala, insula, parahippocampus, orbitofrontal cortex, and ventrolateral prefrontal cortex and anticorrelated to the dorsal anterior cingulate cortex and precuneus. As such the subgenual anterior cingulate cortex could be important as an emotional component for tinnitus.

THE DORSOLATERAL PREFRONTAL CORTEX

Recently the dorsolateral prefrontal cortex has been associated with tinnitus-related distress (Vanneste et al., 2010b). It is known that the dorsal lateral prefrontal cortex has a bilateral facilitatory effect on auditory memory storage (Alain et al., 1998) and contains auditory memory cells (Bodner et al., 1996). The dorsal lateral prefrontal cortex also exerts early inhibitory modulation of input to primary auditory cortex in humans (Knight et al.,

1989) and has been found to be associated with auditory attention (Alain et al., 1998; Lewis et al., 2000; Voisin et al., 2006) resulting in top-down modulation of auditory processing (Mitchell et al., 2005). This was further confirmed by electrophysiological data indicating that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes (Norena et al., 1999). Interestingly, a recent study reported that coupling between dorsal anterior cingulate cortex and the right frontal lobe correlates negatively with tinnitus intrusiveness, which is defined by the authors as how bothersome and obtrusive the tinnitus is perceived (Schlee et al., 2008). However, in the above mentioned study it is not specified which part of the anterior cingulate cortex and prefrontal cortex is involved. Additionally, Jastreboff described the prefrontal cortex as a "candidate for the integration of sensory and emotional aspects of tinnitus" (Jastreboff, 1990). This is in accordance with the idea that the dorsal lateral prefrontal cortex in general could be considered as an area involved in the integration of emotion and cognition (Gray et al., 2002). Nevertheless, further research is needed to clarify the role of the dorsolateral prefrontal cortex in tinnitus.

INSULA

It was shown that the tinnitus questionnaire (TQ) scores are correlated to heart rate rariability markers, and related to neural activity in left and right anterior insula (van der Loo et al., 2011). It was shown that tinnitus distress is related to sympathetic activation, in part mediated via the right anterior insula. In addition the insula is activated in non-coping tinnitus at the alpha frequency band. The left insula is correlated with the TQ at theta, alpha, and gamma frequency band, while the right insula is correlated with delta and gamma frequency band.

The function of the dorsal anterior cingulate cortex and insula might be to integrate motivationally important information with appropriate bodily responses (Critchley et al., 2001) related to the survival needs of the body (Craig, 2003). In addition the insula together with the dorsal anterior cingulate cortex have also been referred to as the salience network (Seeley et al., 2007). This network has been implicated in bottom-up detection of salient events and coordinating appropriate responses (Medford and Critchley, 2010; Menon and Uddin, 2010). Activity in this network is correlated with improved sound detection thresholds, showing a role in the direction of attentional resources toward audition (Sadaghiani et al., 2009). The activation of the salience network suggests that the brain allocates an importance to auditory stimulus and might as such also signify importance to the internally generated tinnitus sound. Activation of the insula and dorsal anterior cingulate cortex during a phantom percept might be considered maladaptive. Imaging studies on the insula associated this area with subjective emotional and bodily awareness (Craig, 2003), as well as interoception (Craig, 2003). The anterior insula has been implicated in autonomic nervous system control (Oppenheimer et al., 1992; Oppenheimer, 1993; Critchley et al., 2004; Critchley, 2005) and might, therefore, be related to the autonomic components involved in distress (Critchley et al., 2000; Wang et al., 2005), induced by the phantom sound. Tinnitus distress is indeed correlated to sympathetic activation, in part mediated via the right anterior insula (van der Loo et al., 2011). Furthermore alpha activity in both the left and right anterior insula was also found for patients with severe tinnitus-related distress who can or cannot cope with these phantom sounds (Vanneste et al., 2010b). Although, the insula seems like an important brain area involved in tinnitus, further research is needed to elucidate what the exact role is of the insula in tinnitus.

THE SUPPLEMENTARY MOTOR AREA

For a sensory stimulus to be consciously perceived, activation of the early sensory areas is a prerequisite but not sufficient (Boly et al., 2005; Dehaene et al., 2006). The (visual) global workspace model suggests conscious perception of sensory events requires sensory cortex activation embedded in a cortical network, the global workspace, extending beyond the primary sensory regions including prefrontal, parietal, and cingulate cortices. Similarly, auditory stimuli need activation of the primary auditory cortex to be consciously perceived. However, this is not sufficient (Laureys et al., 2000; Boly et al., 2005). Studies performed on patients in vegetative state who do not have conscious auditory percepts reveal that auditory stimuli still activate the primary auditory cortex but that there is no functional connectivity to frontal areas in these patients. Primary auditory cortex activation might be only related to loudness coding (Jancke et al., 1998) and not the percept *per se*, similarly to what has been demonstrated at a single-cell level for somatosensory stimuli in the primary somatosensory cortex: stimulus intensity is encoded in the primary somatosensory cortex, while the conscious percept seems to be located in the frontal cortex, more precisely within the supplementary motor area (de Lafuente and Romo, 2005). In addition, Melloni et al., found that theta oscillations in the frontal regions including the supplementary motor area are essential for conscious perception during maintenance interval of visual stimuli (Melloni et al., 2007). Taking these findings together, it can be hypothesized that synchronized gamma activity in the auditory cortex is responsible for the tinnitus loudness (van der Loo et al., 2009), while synchronized theta activity in the supplementary motor area might be accountable for part of the conscious perception of the phantom sound, similar to the conscious perception for somatosensory stimuli.

THE ORBITOFRONTAL CORTEX (INCLUDING THE INFERIOR FRONTAL GYRUS)

Previous research has already shown that orbitofrontal cortex is important for emotional processing of sounds (Wheeler et al., 1993; Damasio, 1996; Dias et al., 1996; Blood et al., 1999). For example, it was revealed that patients with orbitofrontal cortex lesions had reduced self-evaluated perception of the unpleasantness of the acoustic probe stimulus (Angrilli et al., 2008). The orbitofrontal cortex has connections with other limbic areas important for processing of emotion (Beauregard, 2007). Female tinnitus patients have been found to be more emotionally responsive to tinnitus-related distress (Dineen et al., 1997). They also differ in physiological responses to negative emotional stimuli in comparison to males (Bradley et al., 2001; Gard and Kring, 2007). Koch et al. found that an interaction between negative emotion and working memory in females involved activation of the

orbitofrontal cortex, suggesting that during the cognitive control of emotion, females mainly recruit the emotion-associated areas (Koch et al., 2007).

The orbitofrontal cortex together with the insula plays a key role in the top-down modulation of automatic or peripheral physiological responses to emotional experiences (Craig, 2003; Phillips et al., 2003; Critchley et al., 2004; Ohira et al., 2006). More synchronized connectivity between the orbitofrontal cortex and the insula is seen in tinnitus for females. It can, therefore, be hypothesized that the orbitofrontal cortex becomes recruited more often for female tinnitus patients in order to modulate the autonomic physiological responses evoked by tinnitus.

THE POSTERIOR CINGULATE CORTEX AND PRECUNEUS

qEEG data indicate that the posterior cingulate cortex is important in both pure tone and narrow band noise tinnitus (Vanneste et al., 2010a) as well as tinnitus-related distress (Vanneste et al., 2011c). In addition, the precuneus is active within the alpha frequency in patients who can cope with their tinnitus and have a low distress (Vanneste et al., 2011c). Together with the parahippocampal area, activation in the posterior cingulate cortex and precuneus has been associated with the brain's "default" network (Raichle et al., 2001). These regions deactivate when people engage in controlled processing and thought processes. According to this account, default activity is an inverse function of the task demand, where higher demands reduce activity in the default network because mental resources are used to perform a task (Gusnard et al., 2001; McKiernan et al., 2006). As the parahippocampal area as well as the posterior cingulate cortex and precuneus become more active, instead of becoming deactivated during the tinnitus perception, one can hypothesize the tinnitus generators might become integrated in the default mode in tinnitus patients. In addition, the precuneus area is a highly integrative structure, supposed to be involved in visuo-spatial imagery, episodic memory, self-consciousness, and the shifting of attention (Le et al., 1998). The precuneus is also involved in unpleasant music perception (Blood et al., 1999), auditory imagery (Yoo et al., 2001), and auditory memory retrieval (Buckner et al., 1996).

MULTIPLE PARALLEL DYNAMICALLY CHANGING AND PARTIALLY OVERLAPPING SUBNETWORKS

Taking the results in previous sections together the same brain areas occur in the different analyses for tinnitus that are related to different acoustic characteristics such as the tonal nature, lateralization, loudness level, tinnitus duration as well as for the affective components such as distress and mood changes. As such, tinnitus can be seen as the consequence of multiple brain subnetworks involved in the different aspects of tinnitus, both acoustic and affective. Thus, the unified percept of tinnitus, as perceived by the patient, e.g., a loud distressing left-sided pure tone tinnitus, might be considered as an emergent property of multiple parallel dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern signature. This interpretation casts doubts concerning the sole participation of only one critical circuit in phantom perception. Phantom percepts result from auditory deafferentation and reach awareness only when increased neuronal activity in the primary auditory cortex is connected to a larger network involving frontal and parietal areas (De Ridder et al., 2011a). It is possible that different brain subnetworks overlap and might all be involved in how a patient perceives his/her tinnitus.

CONCLUSION

Source localization of qEEG data demonstrate the involvement of auditory brain areas as well as several non-auditory brain areas such as the anterior cingulate cortex (dorsal and subgenual), auditory cortex (primary and secondary), dorsal lateral prefrontal cortex, insula, supplementary motor area, orbitofrontal cortex (including the inferior frontal gyrus), parahippocampus, posterior cingulate cortex and the precuneus, in different aspects of tinnitus. However, few conceptual explanations have been given for all these regions. Evaluating these areas as parts of separable subnetworks, each network representing a specific clinical aspect of tinnitus might help to explain their involvement in tinnitus. Thus, the unified percept of tinnitus can be considered an emergent property of multiple parallel dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature.

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